Progress on Pre-pandemic/Pandemic Influenza Vaccine

M. Tashiro

National Institute of Infectious Diseases, Tokyo, Japan

As pandemic influenza is a matter of global crisis management, WHO has urged to increase international production and supply of pandemic vaccines. For this, each country should establish influenza vaccination policy depending on annual health burden and economical situation. In Asia, while only Japan and China produce seasonal influenza vaccines, several countries including India, Indonesia, Singapore, South Korea, Taiwan, Thailand, and Vietnam, are planning to establish local production of pandemic vaccines. However, pandemic vaccine policy should be based on sustained annual vaccine measures. WHO started to support these countries to implement their local vaccine production of pandemic vaccines. Technical transfer to these facilities by vaccine manufactures in developed countries is essential, but it is conflicting with business and profits of the manufactures.

To develop human H5N1 influenza vaccine, Japan experienced a low immunogenic property in humans of split-type vaccines derived from A/Hong Kong/156/97(H5N1). The Japanese project of H5N1 vaccine development aimed to develop a pandemic vaccine with highly immunogenic and to spare antigens to provide larger population with the vaccines in a short period of time. The WHO prototype vaccine strain, NIBRG-14, propagated in eggs was fixed with formalin. Based on animal experiments, alum-adjuvanted, inactivated whole virus vaccines were prepared. Phase 1 clinical studies followed by Phase 2+3 studies were conducted with 1.75, 5, and 15 mcg HA/dose in one or two doses, and subcutaneously or intramuscularly. Results of the clinical studies showed that the vaccine with 15 mcg HA was tolerable and did not cause severe adverse event. Serum antibody responses were induced efficiently by one or two shots with the high (15) or medium dose (5), respectively, of the vaccines, meeting all of the three EMEA criteria. There results indicated that the inactivated whole virus vaccine conjugated with alum adjuvant is a practically suitable formulation of H5N1 pandemic vaccines. The serum antibody induced by the Clade 1 vaccine cross-reacted significantly with three subclades of Clade 2 viruses.

Based on the data, the Government has introduced national stockpile policy of prepandemic vaccines, now with 20 million courses. Stockpile is to scale-up annually. Before expiration of each batch, vaccination to volunteers of the prioritized groups and then general population is under discussion.

doi:10.1016/j.ijid.2008.05.047

3.001

Clinical Implications of Nasopharyngeal Bacterial Colonization

T. Murphy

University of Buffalo, Buffalo, NY, USA

During childhood, the nasopharynx is colonised by a variety of bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae* (mainly non-typable strains - NTHi) and Moraxella catarrhalis.[1] Generally, nasopharyngeal carriage of these bacteria is asymptomatic. However, under certain circumstances, bacteria in the nasopharynx may cause systemic or localised disease. *S. pneumoniae* is a leading cause of invasive pneumococcal disease (IPD).[1] Elimination of nasopharyngeal pneumococcal colonisation, e.g. by pneumococcal conjugate vaccines, is strongly associated with a reduction in IPD and pneumonia.[2]

The relationship between nasopharyngeal colonisation and otitis media (OM) is more complex. The pathogenesis of OM involves migration of *S. pneumoniae*, NTHi or M. catarrhalis from the nasopharynx to the middle ear. There is a direct relationship between colonisation by pathogens and the first occurrence of acute OM, and colonisation early in life by any of the three pathogens is associated with recurrent OM.[3,4]

S. pneumoniae, NTHi and M. catarrhalis are exclusively human pathogens and occupy the same niche, the nasopharynx, along with ~700 different microbial species. Several mechanisms are involved in establishing and maintaining colonisation and in determining the outcome of competition among strains and species. *S. pneumoniae* and NTHi interact synergistically and antagonistically via mechanisms that include mediators of innate immunity including Toll-like receptors, bacteriocins, hydrogen peroxide production, cell-mediated immunity and complement-dependent phagocytosis.[5–7] A vaccine comprising pneumococcal capsular polysaccharide conjugated to an NTHi surface protein has efficacy in preventing OM caused by both *S. pneumoniae* and NTHi,[8] which provides proof of principle of the feasibility of preventing OM caused by both bacteria. As vaccines are developed and tested, surveillance of nasopharyngeal colonisation will be important because of the critical role it plays in the pathogenesis of OM, pneumonia and other respiratory tract infections.

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doi:10.1016/j.ijid.2008.05.048